Guidance for Industry

CBER Pilot Licensing Program for Immunization of Source Plasma Donors Using Immunogen Red Blood Cells Obtained from an Outside Supplier

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD, 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
June 2000

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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

CBER Pilot: Immunization of Source Plasma Donors Using Immunogen Red Blood Cells Obtained From An Outside Supplier

I. PURPOSE: GUIDANCE SPECIFIC TO THE CBER PILOT

The Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) is proposing a pilot program that would allow a biologics manufacturer to self-certify conformance to licensing criteria prescribed by CBER. The applicability of this particular guidance entitled, "CBER Pilot: The Immunization of Source Plasma Donors Using Immunogen Red Blood Cells Obtained from an Outside Supplier" is limited to the manufacturer of Source Plasma[2] that: (1) holds an unsuspended and unrevoked biologics license for Source Plasma; (2) seeks to supplement the license to include a Red Blood Cells Immunization Program (RBCIP); (3) plans to use immunogen Red Blood Cells (IRBC) obtained per written agreement from an outside supplier, already thawed and deglycerolized; and, (4) has identified an outside supplier of IRBC who holds an unsuspended and unrevoked biologics license for Source Plasma that already includes CBER's authorization for a RBCIP. This guidance is intended to assist those applicants who qualify for and wish to participate in CBER's RBCIP pilot.

II. INTRODUCTION

Pursuant to section 351 of the Public Health Service Act (42 U.S.C. 262 et seq.), all biologic products, including blood and blood components, must be licensed by CBER, FDA prior to being introduced or delivered for introduction into interstate commerce. Traditionally, a manufacturer of blood and blood components obtains a biologics license after CBER's review of the applicant's submission finds that the establishment conforms to the standards prescribed in the regulations and the products are manufactured in a manner that assures safety, purity, and potency. CBER's review of an

[1] This guidance represents FDA's current thinking on a pilot program specific to the immunization of Source Plasma donors using immunogen Red Blood Cells obtained from an outside supplier, either from an outside manufacturer, under a contractual agreement or from an outside facility under the same managerial control as the applicant facility. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. The conventional licensing mechanism or alternative approaches other than this proposed pilot may be used, provided that such approaches satisfy the requirements of the applicable statutes and regulations.

[2] The biologic product name, Source Plasma, is written using capital letters when referring to the licensed final product.

initial application includes a pre-approval inspection. After approval, certain changes in manufacturing methods or intended use of products require the filing of a supplement to each application, the review of which may or may not include a pre-approval inspection. The review of a supplemental application for Source Plasma to include RBCIP does include a pre-approval inspection.

Recently, FDA has streamlined the biologics license application process by consolidating the establishment and product license applications into a single biologics license application (BLA) (October 20, 1999, 64 FR 56441). Additionally, reporting changes to the original approved applications has also been modified by the new requirements under 21 CFR 601.12 (Changes to be Reported; December 1, 1998; 63 FR 66399). Despite these two CBER initiatives, the biologics license application process, supplement preparation, and FDA review remain resource intensive to both the industry and FDA.

With this in mind, FDA is proposing a pilot licensing program that would allow a manufacturer to self-certify conformance to specific criteria as a substitute for CBER's review of information submitted in a BLA supplement. Through this guidance document, FDA is proposing the pilot: the immunization of Source Plasma donors using IRBC obtained from an outside supplier. FDA believes that most manufacturers of IRBC have a positive record of product safety, purity, and potency, and a high level of adherence to current Good Manufacturing Practices (cGMP) regulations (21 CFR parts 210, 211, and 606). This action is intended to reduce unnecessary burdens for industry without diminishing public health protection.

If there is adequate interest in the pilot, FDA will announce its implementation in the Federal Register and will conduct the pilot for approximately one year. At the end of the pilot period, FDA will evaluate the experience in terms of resource efficiency and effectiveness. If the pilot is determined to be efficient and effective without compromising product safety, purity, or potency, FDA intends to allow qualified manufacturers of Source Plasma to continue to pursue the self-certification licensure option.

III. APPLICATION PROCEDURE FOR THE CBER PILOT

A. Applicability

A manufacturer of Source Plasma may, but is not required to, participate in the RBCIP pilot if all of the following conditions are met:

1. The applicant holds an unsuspended and unrevoked license for the manufacture of Source Plasma, issued by CBER under section 351 of the Public Health Service Act;

2. The applicant seeks to supplement the license to include RBCIP;

3. The applicant obtains the IRBC product, already thawed and deglycerolized, from a facility other than the immunizing facility per written agreement;

4. The outside supplier of IRBC holds an unsuspended and unrevoked license for the manufacture of Source Plasma, which includes a RBCIP.

B. Application Contents

The completed application should be submitted to: Director, Office of Blood Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Suite 200N, HFM-99, Rockville, Maryland 20852-1448. The application should include the following:

1. Form FDA 356h: Biologics License Application;

2. A self-certification statement that indicates the manufacturer's compliance with all applicable FDA regulations (i.e., 21 CFR 210, 211, and 600-680) and conformance to CBER licensing criteria outlined in section IV of this guidance;

3. A statement that indicates that the manufacturer is ready for inspection, which means that at least five donors have been immunized;

4. Proposed label(s) for the specific Source Plasma product(s) for which the license supplement is being sought; and,

5. A written request to the Director, CBER, for an exception pursuant to 21 CFR 640.120 from the requirements in 21 CFR 601.12 (b)(3) to submit a detailed BLA supplement. The request should reference the applicant's participation in the pilot program.

IV. SPECIFIC CRITERIA UNDER THE CBER PILOT

Within 90 days of receiving a complete application, CBER will schedule and conduct a pre-approval inspection to verify that the applicant conforms to the following criteria:

A. Medical Oversight and Quality Assurance

1. The applicant's RBCIP must be under the direction and supervision of a qualified licensed physician (21 CFR 640.62, 640.66).

2. The applicant's quality assurance program includes the RBCIP.

B. Standard Operating Procedures

The applicant must develop and maintain standard operating procedures (SOP) (21 CFR 606.100) to control all relevant, specific aspects of product manufacturing, including but not limited to: (1) receipt and storage of IRBC; (2) donor-cell matching and planning the immunization; (3) obtaining informed consent; and (4) donor immunization and monitoring.

1. Receipt and Storage of IRBC

   a. The shipment of IRBC should be evaluated upon receipt to verify: (i) proper shipment temperature of 1 - 10 °C and (ii) accurate product labeling.

   b. The container label should include: (i) the product name; (ii) ABO/Rho(D) blood group designation; (iii) product volume; and (iv) identifying information which allows the tracing of the original IRBC donor, the manufacturing of IRBC, and IRBC product handling.

   c. The label should indicate: (i) storage temperature of 1 - 6 °C; (ii) expiration date; and, (iii) cautionary statement, "For RBC immunization only."

   d. The label should contain the name, address, and registration number of the IRBC manufacturer. The label should not cover the entire

container, to permit visual examination of the contents.

e. IRBC should be stored between 1 - 6 °C to help ensure product purity and integrity of the Red Blood Cells antigens.

2. Donor-Cell Matching and Planning the Immunization

a. A qualified licensed physician should select the Source Plasma donor to receive immunization based on donor considerations that include the following: (i) documentation that future pregnancy is not possible; (ii) pre-existing alloantibodies and the potential to develop new alloantibodies; (iii) response to prior immunizations; and (iv) prior immunization exposure. The applicant should establish an SOP that addresses the inclusion and exclusion criteria to identify potential Source Plasma donors to receive immunization under the RBCIP.

b. Based on records and immunohematologic testing, the qualified licensed physician should match an IRBC to a selected Source Plasma donor in order to minimize the Source Plasma donor's risks for developing unwanted alloantibodies or infectious disease.

c. The qualified licensed physician should plan an immunization schedule specific to the Source Plasma donor, and document the planned immunization schedule. The immunization schedule should be established prior to the first injection, and should be continuously revised based on Source Plasma donor monitoring after each immunization (21 CFR 640.66).

d. The applicant must establish and maintain a donor record file (DRF) for each donor participating in the RBCIP (21 CFR 640.72). For a female donor of childbearing age, the DRF should contain documentation that indicates that future pregnancy is not possible.

e. The selected Source Plasma donor and the donor selection process must satisfy all requirements relevant to the collection of Source Plasma (21 CFR 640.60 - 76). Additional criteria applicable to the RBCIP include the following:

(i) Donors who have not been previously immunized (de novo donors) should be immunized only against Rho(D); immunization with other Red Blood Cells antigens should be limited to donors with the corresponding preexisting alloantibodies.

(ii) The IRBC to be injected into the Source Plasma donor must be typed for ABO/Rho(D) blood groups (21 CFR 640.5), and should be typed for C, c, E, e, K, Fy(a), Fy(b), Jk(a), and Jk(b) Red Blood Cells antigens.

(iii) The considerations in matching IRBC to a Source Plasma donor include: (a) extended Red Blood Cells phenotypes of IRBC and the Source Plasma donor; (b) limiting the Source Plasma donor's exposure to as few IRBC donors as possible; (c) assessing the immunogenicity of IRBC; and, (d) evaluating the immunologic response of the Source Plasma donor.

(iv) The Source Plasma donor should be screened for Red Blood Cells alloantibodies, and an antibody should be identified if detected.

(v) Under the RBCIP, a Source Plasma donor should receive no more than: (a) 4 ml per injection; (b) 5 injections per month; and, (c) 10 injections in a 6-month period. De novo recipients should be given no more than 50 ml of IRBC within any 4-month period. Any recipient not responding after receiving a total of 150 ml of IRBC should be removed from the RBCIP.

(vi) The written immunization schedule must indicate: (a) information about IRBC, including lot and vial information; (b) volume to be administered at each injection; (c) route and site of IRBC injection; (d) the interval for booster immunizations; and, (e) response variables and decision criteria in monitoring the Source Plasma donor following immunization. (21 CFR 606.160).

(vii) The criteria for discontinuing a Source Plasma donor from RBCIP should be clearly established.

3. Obtaining Informed Consent

a. The written consent of a prospective Source Plasma donor must be obtained after a qualified licensed physician explains the hazards of all procedures under the RBCIP to a prospective donor, orally and in writing. The explanation must include the risks of a hemolytic transfusion reaction and the hazards involved in immunization. The explanation must be given in a manner that allows the donor to make an informed voluntary decision to either consent or refuse participation in the RBCIP (21 CFR 640.61).

b. The explanation should include: (i) expected rate of success; (ii) injection volume; (iii) route of administration; (iv) use of subsequent booster immunizations; (v) criteria for discontinuing the program; (vi) an opportunity to ask questions; (vii) the restriction that the donor participates in only one immunization program at a time; and (viii) the advice that the donor may withdraw from the program at any time for any reason.

c. The Source Plasma donor should be informed that testing for antibody detection and identification should continue for a minimum of 12 months after the last immunization as discussed in section IV.B.4.g., irrespective of continued participation in the RBCIP.

d. The Source Plasma donor should be informed of the following possible adverse reactions: (i) local reaction at the injection site, including redness, swelling, and pain; (ii) systemic reaction, including fever, malaise, fatigue, and headache; and, (iii) anaphylaxis, including life-threatening reactions.

e. The Source Plasma donor should be informed that the donor cannot be accepted into the RBCIP if capable of pregnancy. The potential effect of the immunization on future pregnancies and the ability to

receive blood transfusions should be explained.

f. The Source Plasma donor should be informed that although the IRBC is tested there is a potential for developing infectious diseases after immunization by both known and unknown communicable disease agents.

4. Donor Immunization and Monitoring

a. Thawed deglycerolized IRBC should be stored between 1 and 6 °C for a period not to exceed the expiration date indicated on the product label.

b. The IRBC container should be examined prior to use to detect abnormalities, including hemolysis, discoloration, and microbial growth. IRBC not used within four hours after removal from the original container should be destroyed.

c. The injection of IRBC should be performed by a qualified licensed physician or by a qualified person as described in a SOP under the physician's direction. A qualified licensed physician must be on the premises when Source Plasma donors are being immunized with IRBC (21 CFR 640.62 and 640.66).

d. Source Plasma donors should be observed for a minimum of 15 minutes following an IRBC injection.

e. A qualified licensed physician must assess the Source Plasma donor's response to IRBC injections to determine the continued eligibility of the Source Plasma donor under the RBCIP, and evaluate all adverse reactions (21 CFR 640.66).

f. Source Plasma donor monitoring should include: (i) pre-immunization antibody titer; (ii) post-immunization antibody titer; (iii) antibody detection and identification; (iv) cumulative IRBC exposure; and, (v) any adverse reactions to receiving IRBC.

g. A Source Plasma donor should be monitored for a minimum period of 12 months after receiving the last IRBC injection to confirm that the health of the Source Plasma donor has not been unexpectedly affected, including the potential for infectious disease transmission and

the development of Red Blood Cells alloantibodies. All information must be recorded in the DRF (21 CFR 606.160) and the donor should be appropriately counseled as necessary.

h. The applicant should investigate and document in the DRF any unexpected findings with respect to the Source Plasma donor's health related to the use of the IRBC, and should report such finding to the IRBC supplier.

C. Manufacturing Records and Final Product Labeling

Source Plasma collected from a donor immunized with IRBC must be labeled to indicate that the product has been collected from an immunized donor. The label must indicate the immunizing antigen (21 CFR 640.70(a)(7)).

The performance of each step in the manufacturing of Source Plasma under RBCIP must be documented as a part of permanent product records. The manufacturing records must include information regarding IRBC used, and the disposition of Source Plasma collected from immunized donors. All donor-specific information must be documented in the DRF (21 CFR 606.160).

D. Applicant's Oversight of Its Contracted IRBC Supplier

The applicant should establish and maintain procedures to ensure that all IRBC products purchased or otherwise received, conform to standards established by the regulations. The applicant, as a manufacturer, assumes responsibility for compliance with all applicable product and establishment standards (21 CFR 600.3(t)). All provisions considered to be a part of cGMP should be followed by the IRBC supplier. The applicant should: (1) have a mechanism to ensure the periodic review of all records of the IRBC supplier; (2) establish a mechanism to verify that the IRBC supplier performs all appropriate look-back investigations, product withdrawals, and product-related notifications thoroughly and in a timely fashion; and, (3) ensure that all of the IRBC manufacturing procedures including: cryopreservation, deglycerolization, and aliquoting comply with cGMP.

Although this guidance focuses on the responsibilities of the applicant after receiving

IRBC from an outside supplier, the applicant shall establish and follow procedures for receipt, identification, storage, handling, sampling, testing, and approval or rejection of IRBC from an outside supplier (21 CFR 211.80). If the applicant's assessment of an outside supplier's manufacturing procedures suggests that the manufacturing, storage, and shipping procedures used by the supplier do not comply with cGMP or compromise or potentially compromise the safety, purity, and potency of IRBC the applicant should either ensure adequate corrective action or terminate receiving IRBC from that supplier. The applicant should maintain an updated record of oversight activities for review at FDA inspections.

The applicant should ensure that IRBC donors are selected by the IRBC supplier according to all applicable donor suitability requirements, and that IRBC are qualified for routine use according to the criteria set forth below:

1. All requirements applicable to donors of Red Blood Cells for transfusion use also apply to the prospective IRBC donor. The IRBC supplier should test the IRBC donor for all infectious diseases as required (21 CFR 610.40, 610.45, 640.5) and recommended by the FDA in manufacturing blood components for transfusion use. Only those Red Blood Cells collected from donors whose test results are negative may proceed towards cell qualification. All applicable tests should be performed using FDA approved test kits.

2. The collected Red Blood Cells should be cryopreserved and stored under quarantine for at least 12 months, after which time the IRBC supplier retests the cell donor to confirm that the donor has not seroconverted for any of the infectious disease tests required and recommended by FDA.

3. In order to qualify Red Blood Cells, the IRBC supplier should select up to 3 recipients for the initial immunization use of the collected Red Blood Cells. The selected recipients should not have a history of exposure to Red Blood Cells within the 12 months prior to the intended immunization. The IRBC supplier should test the recipients to confirm that they are negative for infectious disease tests required and recommended by FDA. The initial immunizations should proceed only if all testing and historical requirements have been met. Red Blood Cells phenotyping including, but not limited to, ABO/Rho(D), C, E, e, K, Fy(a), Fy(b), Jk(a), and Jk(b) Red Blood Cells antigens should be performed on both cell donors and recipients, and the

results should be used in matching the cells to the appropriate recipients. Additionally, sterility testing should be performed on the cells and the results should be negative prior to using the cells. Test methods should be consistent with the reagent manufacturer's directions.

4. The recipients of the cells undergoing qualification should be observed for at least 12 months subsequent to immunization, with periodic recipient testing at 3, 6, 9, and 12 months. All testing should be negative throughout the 12-month period in order to declare the collected Red Blood Cells as qualified IRBC.

5. The cell qualification process should be completed before proceeding with any additional cell processing, labeling, or shipment of the IRBC. Final containers for the IRBC product should be sterile, pyrogen-free, single dose vials that have been deemed suitable by FDA. IRBC should be aliquotted into the final containers using sterile techniques.

6. Immunizations should be evaluated for safety, effectiveness, and for the development of unexpected antibody responses. A Red Blood Cells donor is considered to be a qualified IRBC donor once cells collected from the donor have been successfully qualified as IRBC and no available information otherwise disqualifies the donor. If Red Blood Cells are collected from a qualified IRBC donor, the cell qualification procedure is limited to the following.

    a. The qualified IRBC donor should be tested at cell collection for all required/recommended tests, and all results should be negative.

    b. The cells should be collected, cryopreserved, and stored under quarantine for at least 12 months. The qualified IRBC donor should be retested at the end of the cell quarantine period for all required/recommended tests, and all results should be negative.

7. The procedures and controls used in the manufacturing of IRBC should be outlined clearly in the IRBC supplier's SOPs. The procedures should be sufficiently detailed to assure safety, purity, and potency of the IRBC product. The applicant should determine that the manufacturer of the IRBC has an

adequate quality assurance program, including appropriate SOPs for implementation and continuous quality assurance functions, prior to entering into an agreement to obtain IRBC from the manufacturer.

V. REFERENCES

1. FDA Memorandum, "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products," April 23, 1992.

2. Merryman, H.T. and Hornblower, M.A., "A method for freezing and washing RBC in a high glycerol concentration," Transfusion (1972): 12:145-56.

3. Merryman, H.T. and Hornblower, M.A., "A Simplified Procedure for Deglycerolizing Red Blood Cells Frozen in a High Glycerol Concentration," Transfusion (1977): September-October.

4. Food and Drug Administration, Bureau of Biologics, Division of Blood and Blood Products, "Guidelines for Immunization of Source Plasma (Human) Donors with Blood Substances," Revised, June 1980.

5. FDA, Compliance Policy Guide: Source Plasma Guidelines for Informed Consent Forms, August 1996.

6. FDA Memorandum, "Control of Unsuitable Blood and Blood Components," April 6, 1988.

7. Food and Drug Administration, Center for Biologics Evaluation and Research, "Guidelines for Quality Assurance in Blood Establishments," July 11, 1995.

8. FDA Memorandum, "Revised Recommendations for Red Blood Cells Immunization Programs for Source Plasma Donors," March 4, 1995.